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Review

Air Pollution Exposure as a Relevant Risk Factor for COPD Exacerbations in Male and Female Patients

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Abstract: Chronic obstructive pulmonary disease (COPD) is a multifactorial lung inflammatory disease affecting 174 million people worldwide, with a recently reported increased incidence in female patients. Patients with COPD are especially vulnerable to the detrimental effects of environmental exposures, especially from air particulate and gaseous pollutants. Exposure to air pollution severely influences COPD outcomes, resulting in acute exacerbations, hospitalizations, and death. In the current study, we conducted a review of the literature addressing air pollution induced acute exacerbations of COPD (AECOPD) in order to determine whether air pollution affects COPD patients in a sex-specific manner. We found that while the majority of studies enrolled both male and female patients, only a few reported results disaggregated by sex. Most studies had a higher enrollment of male patients, only four compared AECOPD outcomes between sexes, and only one study identified sex differences in AECOPD, with females displaying higher rates. Overall, our analysis of the literature confirmed that air pollution exposure is a trigger for AECOPD hospitalizations and revealed a significant gap in our knowledge of sex-specific effects of air pollutants on COPD outcomes, highlighting the need for more studies considering sex as a biological variable.

Keywords: COPD exacerbation; air pollution; hospital admission; sex differences

1. Introduction

1.1. COPD Definition

Chronic Obstructive Pulmonary Disease (COPD) is a lung inflammatory disease that includes emphysema and chronic bronchitis and is characterized by airflow blockage in the lungs [1]. The diagnosis of COPD includes spirometry values of less than 70% of predicted forced expiratory volume (FEV) that is incompletely reversible with the administration of an inhaled bronchodilator. Pathological features are observed in central airways, small airways, and alveolar spaces. The pathogenesis of COPD includes proteinase-antiproteinase imbalance, immunological mechanisms, oxidant-antioxidant balance, systemic inflammation, apoptosis, and ineffective repair, and accelerated decline in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) [1]. Airflow limitation in COPD is defined as a post-bronchodilator FEV1 to FVC ratio of 0.70 or lower. The diagnosis of COPD is also determined on the basis of symptoms and signs (e.g., exertional breathlessness, chronic cough, regular sputum production, frequent bronchitis, or wheeze, etc.) in people over 35 years of age who have a risk factor (e.g., smoking history), although these clinical findings have to be supported by spirometry, as defined by GOLD and NICE standards.

The development of COPD is multifactorial, and the risk factors include genetic, environmental, and sex and gender factors. While cigarette smoke is the most critical risk factor associated with COPD, occupational and other environmental exposures are known to cause approximately one in six cases [2]. Female sex and gender have also been

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independently associated with COPD development due to differential susceptibility to lung-damaging effects of cigarette smoking [3], interactions of female hormones with toxins present in tobacco products, and other factors such as exposure to household air pollution and environmental triggers [4,5].

1.2. Epidemiology

COPD affects approximately 17.4 million people (7.3 million males vs. 10.1 million females) in the United States [6], and an estimated 174 million (104.3 million males and 69.7 million females) worldwide [7]. It is the fourth-leading cause of death and the fourth leading cause of chronic disease–related morbidity and mortality, accounting for more than 120,000 deaths annually in the United States and 3.2 million globally [7,8]. Several research studies have suggested that outdoor air pollution exposure is linked to the prevalence and incidence of COPD [9].

In the past few decades, the prevalence of COPD among women has significantly increased, from 50.8 to 58.2 per 1,000 people, while in men it has decreased from 108.1 to 74.3 per 1,000 people [10]. More recent data indicate that that the COPD prevalence was higher among women than men between 1998-2009 [2]. In addition, since the year 2000, the number of women dying from COPD has also surpassed the number of men [11,12]. These trends are partially explained by the higher susceptibility of women to the negative effects of smoking, which results in earlier development of severe forms of the disease, as well as historical differences in tobacco use, environmental and occupational exposures, and bias in disease diagnosis [13,14].

1.3. Air quality as a risk factor

Air pollution exposure is estimated to contribute to approximately 7 million early deaths every year worldwide and more than 3% of disability-adjusted life years lost [15]. Air pollution has numerous harmful effects on health and contributes to the development and morbidity of cardiovascular disease, metabolic disorders, and a number of lung pathologies, including asthma and COPD [16]. To this end, air pollution is the world's most extensive single environmental risk, according to the World Health Organization.

Recently, it has been found that the number of patients with COPD who do not have a history of smoking is higher than expected [17], particularly female patients [18]. Emerging data indicate that air pollution exposure alters epigenetic markers, such as DNA methylation (DNAm) and that these changes may influence the expression of genes that control inflammation, disease development, and exacerbation risk [19,20]. Exposure to several traffic-related air pollution (TRAP) components, including particulate matter (PM), black smoke (BS), ozone (O_3), nitrogen oxides (NOx), and polyaromatic hydrocarbons has been associated with changes in DNAm in lung and other tissues [20,21]. Air pollution exposure can also stimulate pro-inflammatory immune responses, including T helper lymphocyte type 2 (Th2) and type 17 (Th17) adaptive responses, and dysregulate anti-viral immune responses [22,23]. The clinical effects of acute and chronic air pollution exposure, in particular the known association between elevated levels and exacerbations of asthma and COPD, are consistent with those identified in inflammatory and immunological mechanisms activated in the lung during disease processes [24]. For example, short-term exposure to air PM, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) can trigger a neutrophil-mediated airway inflammatory response, followed by increased clinical symptoms [25]. The deposition of PM in the respiratory tract depends predominantly on the size of the particles, with larger particles deposited in the upper and larger airways and smaller particles penetrating deep into the alveolar spaces. Ineffective clearance of PM from the airways could cause particle retention in lung tissue, resulting in a chronic, low-grade inflammatory responses that may be pathogenically important in both the exacerbation and progression of lung disease [26].

Globally, exposure to household indoor air pollution in women who do not smoke also occurs via inhalation of combustion products from biomass fuels, including wood,

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charcoal, animal dung, and others used for cooking [27,28]. Due to traditional gender roles, these exposures have significantly contributed to COPD morbidity and mortality in women [29]. It is estimated that 50% of households worldwide (about 3 billion people) are exposed to smoke from biomass fuel combustion. These exposures contribute to about half of the deaths from COPD in developing countries, of which 75% are women [27,28].

1.4. Exacerbation triggers

Exacerbations of COPD are episodes of worsening of symptoms, leading to substantial morbidity and mortality [30]. COPD exacerbations are associated with increased airway and systemic inflammation and physiological changes, including hyperinflation. These are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. Some patients are particularly susceptible to exacerbations and show worse health status and faster disease progression than those who have infrequent exacerbations [31].

The mechanisms of COPD exacerbations are complex. While respiratory viruses (in particular rhinoviruses) and bacteria play a major role in their causative etiology [32], in some patients, noninfective environmental factors also contribute to their development. Data recently published from a large observational study identified a phenotype of patients that are more susceptible to frequent exacerbations from environmental exposures [33]. Other quantitative studies indicated that anxiety and depression could lead to a statistically significant increase in the likelihood of COPD patients being hospitalized [34]. Although more than 80% of exacerbations are managed on an outpatient basis, hospitalization is all too common and associated with considerable health care costs and mortality. In this regard, noninvasive ventilation has greatly decreased the mortality in exacerbations that require ventilatory support. However, across the range of exacerbation severity, treatment failure and relapses are frequent [35].

Among individuals with COPD, exposure to outdoor air pollutants is associated with loss of lung function and increased respiratory symptoms, leading to exacerbations and increased mortality [36]. Some studies suggest that temperature may modify the effect of air pollution exposure, although their results are not conclusive [37]. For example, Yan *et al.* explored the environmental effect of two different geographical places on COPD exacerbations (Beijing in summer, Sanya in winter) and found that poorer air quality index (AQI) and higher temperatures in Beijing were associated with lower FEV1, higher dyspnea, and a twice higher relative risk of exacerbations than in patients in Sanya [38]. The authors also reported that ambient air pollution was strongly associated with COPD exacerbations by triggering apoptosis in airway epithelial cells [38].

Although adequate evidence for a direct relationship between ambient air pollution components and the development of COPD is lacking, higher mortality rates from respiratory and cardiovascular diseases have been reported among patients exposed to air pollution for a very long time [19,39]. Several reports have also pointed out the possibility that acute exacerbations of COPD can be caused by short-term exposures to air pollutants [25,40,41], as well as secondhand tobacco smoke [42].

Regarding sex differences in COPD exacerbations, the available literature indicates that outdoor air pollution affects lung function and triggers exacerbations in both male and female patients, but nonsmoker women may be more affected than men [11,43,44]. This indicates that air pollution may result in differential COPD exacerbation rates and outcomes in men vs. women. Data from multi-center studies have also shown that air pollution concentrations in the ambient are associated with declined lung function and increased risks for hospitalization and mortality in COPD patients. Because sex differences in AECOPD is an understudied area, in the current review, we investigated the association between exposure to gaseous and particulate pollutants and hospitalizations for COPD exacerbations, paying particular attention to differences between males and females. Other systematic reviews and meta-analyses have found that short-term exposures to air pollutants significantly increase the burden of risk of COPD acute exacerbations

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[4,45]. In the current study, we focus on the association of air pollution exposure and hospitalizations for COPD exacerbations with an emphasis on sex differences. Therefore, we selected studies that included both male and female participants, including those that did or did not analyze outcomes by sex.

2. Materials and Methods

2.1. Literature Search, Databases and Key Terms Searched

We used PubMed and Google Scholar to search for articles related to our study's focus, using the following search terms: "air pollution", "COPD", "COPD exacerbation", "hospital admission", and "sex". The search was limited to epidemiological studies from 2000 to 2020, although we also included articles prior to 1990 if they contained relevant information. We focused on articles that pooled results on a global scale, reported analytical pooled estimates, were written in English or with an English abstract and studied associations between air pollution and hospitalization for COPD exacerbation as well as respiratory response to shorter-term exposure of air pollution.

2.2. Inclusion Criteria

The literature search was limited to human epidemiological studies on (1) Hospitalization due to acute exacerbation of COPD, as identified by the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes J40-J44; (2) A diagnosis of COPD; and presentation for treatment of acute exacerbations of COPD (AECOPD), as defined by increasing shortness of breath, worsening cough, or change in sputum production at presentation; (3) Research-data based; (4) From adult patients (age > 18 years); and (5) published in English language.

2.3. Search Process and Study Selection

PubMed and Google Scholar were the main databases utilized. Records were de-duplicated using built-in mechanisms of university library services (Covidence software) and further completed manually. Articles were then screened by their titles and abstracts for inclusion or exclusion. Final selections were determined after full reading of articles.

2.4. Data Extraction and Analysis

We extracted information on the association between daily mean concentrations of particulate matter of a diameter of less than 10μm (PM_{10}) or 2.5μm ($PM_{2.5}$) as well as other gas pollutants (O_3, CO, NO_2, SO_2) with hospital admissions, analyzing the sex variable, based on daily measurements reported in each study or other data that could be aggregated into daily mean values. Thus, results are presented as associations of 24-hour average air pollutant concentrations and daily hospital admissions for AECOPD.

3. Results

3.1. Selected studies

A flow chart of the literature search is shown in **Figure 1**. The search string returned 8,302 potentially relevant article citations. After systematically reviewing all the abstracts, 7,014 irrelevant studies and 1,083 duplicates were removed. The two authors independently reviewed the remaining 205 full articles for inclusion. After full-text revision, 40 articles were included for systematic analysis and are summarized in **Table 1**. Combined, these articles reported a total of 2,329,320 hospital admissions for AECOPD, with an average of 58,233 hospitalizations per study ranging from 40 to 578,006 and a standard

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deviation of 134,419. Hospitalizations for AECOPD in the selected studies spanned four different continents, and the statistics per continent are shown in **Figure 2.**

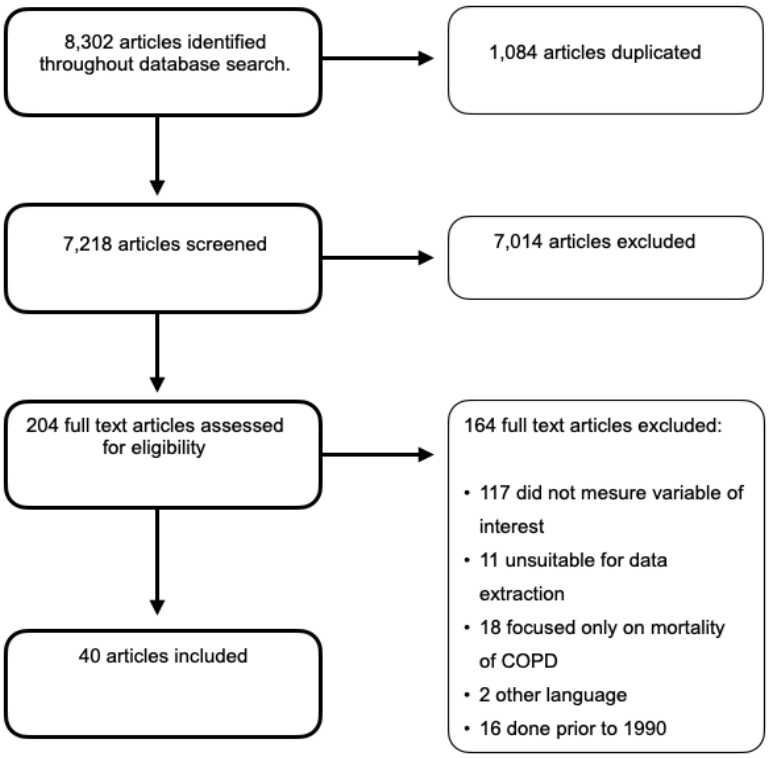

Figure 1. Literature search flow for this study.

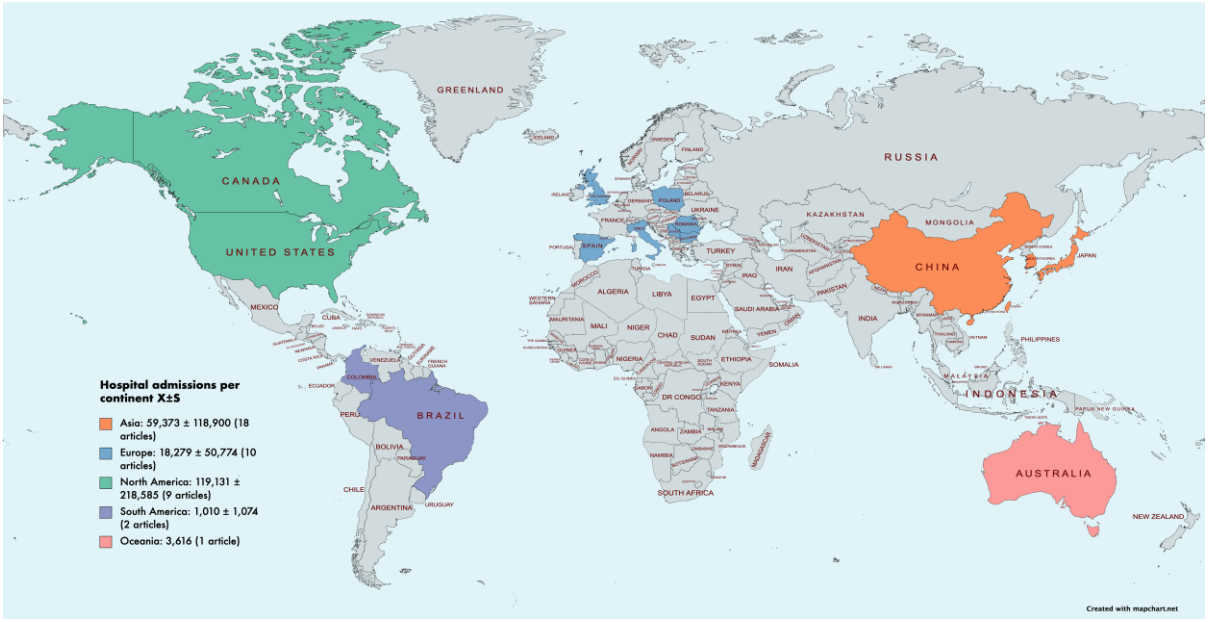

Figure 2. Geographical distribution of studies assessing hospitalization for AECOPD due to air pollution.

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3.2. Individual and combined air pollutant concentrations and their association to daily hospital admissions for AECOPD

Table 1 summarizes the effects of air pollution of exposure in AECOPD in 40 studies. Regardless of geographical location, most studies identified a significant association between particulate pollution exposure and AECOPD. The incremental increases in concentrations of $PM_{2.5}$ and PM_{10} were significantly associated with increased risk of hospitalization of AECOPD [40,46], but also stroke and myocardial infarction. However, the adverse influences of $PM_{2.5}$ on these diseases were generally more robust than those of PM_{10} [47]. In the US mid-Atlantic states, $PM_{2.5}$ exposure was associated with all COPD hospital admissions, with a relative risk increase of 1.83 for every 10μg/m^3 increase in $PM_{2.5}$ [46]. In Central and Eastern Europe, increases in hospital admissions were reported as 3.3% and 2.8% for PM_{10} and $PM_{2.5}$, respectively [48].

When assessing the effects of gaseous air pollutants on AECOPD, it was found that SO_2 increases of 10μg/m^3 were related to a 6% increase in hospital admissions for chronic bronchitis, with a two-day lag [49]. Comparably, an independent air pollution modeling study found that when modeled jointly with other pollutants, only SO_2 remained significantly associated with AECOPD (hazard ratio 1.038), although the five pollutants assessed in this study were highly correlated (r = 0.89) [48]. In addition, short-term exposures to SO_2 were associated with an increase in COPD exacerbation risk, with an odds ratio (OR) of 2.45 per 1 ppb increase in SO_2 levels, after adjustment for $PM_{2.5}$ in a region with a relatively low AQI (central Massachusetts, USA) [41]. Regarding NO_2 and CO, both were significantly associated with AECOPD hospitalizations [50]. Tellingly, the magnitude of effects was expanded slightly with increasing days of exposure, with a relative risk of 1.11 and 1.08 for NO_2 and CO, respectively, for a 7-day exposure average [50]. Likewise, a study in South Korea found that each 10μg/m^3 increase in CO was associated with a 2% increase in the odds of admission for AECOPD [51].

In multi-pollutant exposure models, significant associations between hospital admissions for COPD were found for all five air pollutants (SO_2, NO_2, O_3, PM_{10}, $PM_{2.5}$), with relative risks for admission for every 10μg/m^3 increase of SO_2 = 1.007, NO_2 = 1.026, O_3 = 1.034, PM_{10} = 1.024, and $PM_{2.5}$ = 1.031, respectively, at a lag day ranging from lag 0 to cumulative lag 0-5 [52]. PM_{10} and SO_2 were associated with both acute and lagged effects on emergency department visits due to COPD, with interquartile range increases in 28.3μg/m^3 and 7.8μg/m^3, respectively, associated with a cumulative 6-day increase of 19% and 16% in COPD admissions, respectively [53]. In addition, declines in attributable hospital admissions for AECOPD were associated with a reduction in concentrations of $PM_{2.5}$, PM_{10}, SO_2, and O_3 [54].

Finally, other environmental factors have been found to contribute to AECOPD in the studies analyzed. For example, the COPD-related emergency room admissions for all age groups were significantly associated with previous-day BS levels, and lag 0-2 (1.60% and 2.26% increase per 10μg/m^3, respectively) in a study conducted in Serbia [55]. Similarly, a study in Guangzhou, China, found that haze (at lag1) and air pollution (NO_2 at lag 5 and SO_2 at lag 3 combined presented more drastic effects on patients aged 19-64, especially in females [56]. Increases in NO_2 were associated with the highest risk of hospital admissions for total and respiratory diseases in both single- and multi-pollutant models, and a relative risk of 1.94 in ER at lag 0 for COPD patients [56]. Relative risks at lag0 ranged from 1·018 to 1·036 for each interquartile range increase in air pollution concentration. These increased risks became non- significant by lag4 [56].

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Table 1. Studies reporting acute exacerbation of COPD due to air pollution exposure

Reference	Study Type	Pollutants	Period & Location	Total sample (N) M:F Age	Measured Outcome	Main Findings
Ko *et al.*, 2007 [52]	Time-series study	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3	2000-2004 Hong Kong	119,225, M:F(N/A) >18 years	Hospital Admissions	Ambient concentrations of air pollutants increased hospital admissions for COPD, especially during the winter season (December-March), where indoor exposure to air pollution was higher.
Qiu *et al.*,2012 [57]	Time-series study	$PM_{2.5}$, PM_{10}	2000-2005 Hong Kong	2,192 M:F(N/A) >18 years	Hospital Admissions	PM_{10} exposure was significantly associated with ED admissions for respiratory diseases, independently of other pollutants.
Kloog *et al.*,2014 [46]	Case-crossover analysis	$PM_{2.5}$	2000-2006 United States	416,778 176,314 M:240,464 F ≥65 years	Hospital Admissions	$PM_{2.5}$ exposure was associated with all COPD hospital admissions with an increased RR of 1.83 for every 10μg/m^3 increase in $PM_{2.5}$.
Leitte *et al.*,2009 [49]	Time-series study	TSP, SO_2, NO_2	2001-2002 Romania	671 M:F(N/A) >18 years	Hospital Admissions & Mortality	Chronic bronchitis was associated with particulate matter and mainly SO_2, and dry air aggravates the adverse effect of particulate matter.
Arbex *et al.*,2009 [53]	Time-series study	PM_{10}, CO, SO_2, NO_2, O_3	2001-2003 Brazil	1,769 975 M:794 F ≥40 years	Hospital Admissions	PM_{10} and SO_2 readings showed both acute and lagged effects on COPD ED visits. Increases in CO concentration showed impacts in the female and elderly groups.
Tao *et al.*,2014 [58]	Time-series study	PM_{10}, SO_2, NO_2	2001-2005 China	5,301 M 3,663:F 1,638 >18 years	Hospital Admissions	There were significant associations between air pollutants exposure and respiratory hospital admissions, and stronger effects were observed for females and patients aged ≥65 years
Tian *et al.*,2014 [59]	Time-series study	$PM_{2.5}$, CO, NO_2	2001-2007 Hong Kong	117,329 M:F(N/A) >18 years	Hospital Admissions	Ambient CO was negatively associated with the risk of hospitalizations for COPD. After adjustment for NO_2 or $PM_{2.5}$ levels, the negative associations of CO with COPD hospitalizations became stronger.

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Milutinović *et al.*,2009 [55]	Time-series study	BS, SO_2	2002-2003 Serbia	4,572 M:F(N/A) >18 years	Hospital Admissions	The ED admissions for all ages for COPD were significantly associated with previous-day levels of BS and lag 0-2. After controlling for SO_2, single lagged (lag 1 and lag 2) as well as mean lagged values of BS (up to lag 0-3) were significantly associated with COPD ED visits.
Chen *et al.*,2004 [60]	Time-series study	$PM_{2.5}$, PM_{10}	1995-1999 Canada	4,409 M:F(N/A) ≥65 years	Hospital Admissions	PM measures were significantly associated with COPD hospitalization in areas where the level of air pollution are relatively low. The effects were not independent of other air pollutants.
To *et al.*,2015 [61]	Time-series study	$PM_{2.5}$, PM_{10}, NO_2,O_3	2003-2010 Canada	21,334 M:F(N/A) >18 years	Hospital Admissions	The greatest increases in hospital admissions were for individuals with diabetes and COPD. Among individuals with chronic diseases, health service use increased with higher levels of exposure to air pollution, as measured by the AQHI.
Cho *et al.*,2014 [51]	Case-crossover analysis	PM_{10}, CO, SO_2, NO_2, O_3	2005-2009 Korea	842 M:F(N/A) >18 years	Hospital Admissions	After stratification by underlying disease, PM_{10}, NO_2, and CO were positively associated with ED visits for depressive episodes in each disease strata with the exception of COPD. SO_2, PM_{10}, NO_2, and CO significantly increased the risk of ED visits for depressive episodes, especially among individuals with pre-existing cardiovascular disease, diabetes mellitus, or asthma.
Sauerzapf *et al.*,2009 [62]	Case-crossover analysis	$PM_{2.5}$, CO, NO_2, NO_X, O_3	2006-2007 England	1,050 M:F(N/A) >18 years	Hospital Admissions	Among a population of a less urbanized area, this study found evidence that ambient pollutant concentrations were still associated with the risks of hospital admission for COPD.
Cai *et al.*,2015 [63]	Time-series study	CO	2006-2008 China	121,463 M:F(N/A) >18 years	Hospital Admissions	Negative associations were found between ambient CO concentrations and daily COPD hospitalization. An interquartile range increase of 0.6 mg/m^3 in CO concentration at lag 3 day corresponded to -2.97% (95% confidence interval: -4.63%, -1.31%) change in COPD hospitalization. Short-term exposure to CO at low ambient

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						concentration may be associated with reduced risk of COPD hospitalization.
Yorifuji *et al.*,2014 [64]	Case-crossover analysis	SPM, O_3, SO_2	2006-2010 Japan	767 M:F(N/A) ≥65 years	Hospital Admissions	SPM exposure 24 to < 72 hours prior to the onset, and O_3 exposure 48 to < 96 hours prior to the onset were associated with increased risk of respiratory disease. Hourly changes in air pollution exposure increased the risk of respiratory disease, and SO_2 may be related with more immediate effects than other pollutants.
Schikowski *et al.*,2014 [65]	Case-crossover analysis	PM, NO_X	2006-2010 Taiwan	10,242 4,348 M:5,894 F >18 years	Hospital Admissions	The only statistically significant associations were observed in females (COPD prevalence using GOLD: OR 1.57, 95% CI 1.11–2.23; and incidence: OR 1.79, 95% CI 1.21–2.68). None of the principal results were statistically significant.
Zhang *et al.*,2014 [56]	Time-series study	Haze, SO_2, NO_2	2008-2011 China	1,380 M:F (N/A) >18 years	Hospital Admissions	NO_2 was the sole pollutant with the largest risk of hospital admissions for total and respiratory diseases in both single- and multi-pollutant models and both presented more drastic effects on the 19 to 64 years old and in females. Haze pollution was associated with total and cardiovascular illnesses.
Yan *et al.*,2019 [66]	Comparative study	PM, CO	2016-2018 China	139 48 M:91 F >18 years	Hospital Admissions	These findings suggested that ambient air pollution causes COPD exacerbation, and that PM exposure induces apoptosis of airway epithelial cells.
Liang *et al.*,2019 [67]	Ecological analysis	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3	2013-2017 China	161,613 M:F(N/A) >18 years	Hospital Admissions	Increased acute air pollution episodes were significantly associated with increased hospitalizations for AECOPD with women and patients aged > 65 years showing the highest susceptibility and hospitalization risk.

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Hendryx *et al.*,2019 [48]	Longitudinal study	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2	2000-2019 Australia	3616 all female >18 years	New COPD cases	Controlling for covariates, all five air pollutants modeled individually were significantly associated with risk of COPD. Multiple exposure sources and pollutants contributed to COPD risk, including electricity generation and mining but extending to many industrial processes.
DeVries *et al.*,2016 [41]	Case-crossover analysis	$PM_{2.5}$, SO_2, NO_2	2011-2012 United States	168 57 M:101 F ≥65 years	Hospital Admissions	Short-term exposures to SO_2 were associated with an increase in COPD exacerbation risk OR 2.45 (95 % CI: 1.75-3.45 per 1 ppb increase) after adjustment for $PM_{2.5}$. Despite living in areas with air pollution concentrations below current USEPA NAAQS, these COPD patients appeared to suffer increased risk of COPD exacerbation following short-term exposures to increased SO_2 and NO_2 levels.
Du *et al.*,2021 [68]	Time-series study	SO_2, CO, PM_{10}, $PM_{2.5}$, O_3, NO_2	2019 China	1,563 1,277 M:286 F ≥65 years	Hospital Admissions	The concentrations of 6 monitored pollutants and AECOPD hospitalizations showed statistically significant spatial clustering. After adjusting for potential confounders, residential SO_2, NO_2 and O_3 concentrations were significantly associated with increased AECOPD hospitalizations. Ambient air pollution was spatially correlated with AECOPD hospitalizations.
Lin *et al.*,2018 [69]	Case-crossover analysis	NO_2, CO, SO_2, PM_{10}, $PM_{2.5}$, O_3	2011–2015 Taiwan	277 240 M:37 F ≥65 years	Hospital Admissions	Increased NO_2, CO, O_3 and PM_{10} concentrations and continual temperature changes (colder during cooling-down seasons or hotter during warming-up seasons) were associated with AE COPD in older patients.
Sinharay *et al.*,2017 [70]	Randomized, crossover study	BC, NO_2, PM_{10}, $PM_{2.5}$, UFP	2012-2014 United Kingdom	40 19 M:21 F ≥60 years	Respiratory response to shorter-term exposure of air pollution	Participants with COPD reported more cough (OR 1·95, 95% CI 0·96-3·95), sputum (OR 3·15, 95% CI 1·39-7·13), shortness of breath (OR 1·86, 95% CI 0·97-3·57), and wheeze (OR 4·00, 95% CI 1·52-10·50) after walking down Oxford Street (high traffic pollution) compared with Hyde Park (low traffic pollution).

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Wang *et al.*,2021 [54]	Ecological study	$PM_{2.5}$, PM_{10}, PMcoarse, SO_2, NO_2, CO, O_3	2013-2017 China	483,861 M:F(N/A) >18 years	Hospital Admissions	Reduction in PM may result in declined attributable hospitalizations for AECOPD, while O_3 is an important risk factor following an intervention.
Chen *et al.*,2020 [71]	Time-series study	$PM_{2.5}$, PM_{10}, SO_2, NO2, O_3	2014-2017 China	17,655 9,234 M:8,421 F >18 years	Hospital Admissions	Air pollution increased the rate of hospitalization for AECOPD. The risk of hospitalization for AECOPD in the age ≥65 group was greater than age < 65 group for all day lags. The risk of male and female hospitalizations for AECOPD after lag3–lag5 was higher than that after lag0–lag2, and the strongest risk of hospitalizations for both was with lag3.
Zieliński *et al.*,2018 [72]	Time-series study	$PM_{2.5}$, PM_{10}	2006-2016 Poland	12,889 7968 M:4921 F ≥65 years	Hospital Admissions	No connection between PM_{10} concentration and COPD exacerbations were observed. The $PM_{2.5}$ influence was significant beginning on 14 day before admission (RR 1.06) and increased up to a maximal studied period of 90 days (RR 1.32).
Gutierrez *et al.*,2020 [73]	Prospective cohort study	$PM_{2.5}$	2013-2016 United States	296 290 M:6 F ≥65 years	Hospital Admissions	Saharan dust outbreaks observed in Miami elevated the concentration of PM and increased the risk of AECOPD in patients with recurrent exacerbations.
Chen *et al.*,2019 [47]	Time-series study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	2013-2015 China	6,981 4,920 M:2,061 F ≥65 years	Hospital Admissions	The incremental increased concentrations of $PM_{2.5}$ and PM_{10} were significantly associated with increased risk of hospitalization of AECOPD, stroke, and MI, and the adverse influences of $PM_{2.5}$ on these diseases were generally stronger than that of PM_{10} in Jinan, China.
Chen *et al.*,2019 [74]	Time-Series study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	2014-2018 China	17,592 9,196 M:8,396 F >18 years	Hospital Admissions	Air pollution, relative humidity, and temperature increased the risk of admission for AECOPD. The effect of O_3 on the admission rate in male group was higher than that in the female group. Ambient air pollution had a weak influence on the age ≤ 50 group.

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Kwon *et al.*,2020 [75]	Cohort study	PM_{10}, NO_2	2012-2017 Korea	296 238 M:58 F ≥65 years	Respiratory response to shorter-term exposure of air pollution	Long-term exposure to PM_{10} correlated with both lung function and COPD-relevant imaging phenotypes in a Korean cohort.
Pini *et al.*,2021 [40]	Time-series study	$PM_{2.5}$, PM_{10}	2014-2016 Italy	431 M:F(N/A) Age: N/A	Hospital Admissions	Short-term increases in exposure to PM_{10} or $PM_{2.5}$ were associated with a higher risk of ED admission and hospitalization due to AECOPD with a greater incidence during the winter season.
Reid *et al.*,2019 [76]	Cohort study	$PM_{2.5}$, O_3	2008 United States	4,614 M:F(N/A) >18 years	Hospital Admissions	There were more ED visits than hospitalizations during the study period. For $PM_{2.5}$, increasing risk of asthma hospitalizations with increasing quintiles of exposure was found in the $PM_{2.5}$-only model and the mutually adjusted model. ED visits for asthma, and COPD increased with increasing quintiles of $PM_{2.5}$ exposure.
de Miguel-Díez *et al.*,2019 [77]	Case-crossover study	NO_2, O_3, PM_{10}, CO	2004 -2013 Spain	162,338 135,598 M:26,740 F ≥65 years	Hospital Admissions & mortality	Significant associations of temperature, humidity, O_3, CO, PM_{10} NO_2 with hospital admissions were identified.
Stevanović *et al.*,2016 [78]	Cohort study	$PM_{2.5}$	2011 Serbia	270 181 M:89 F (>18 years)	Hospital Admissions	The number of days with high levels of $PM_{2.5}$ per month was significantly associated with the total number of exacerbations (moderate and severe) for both asthma and COPD episodes among female and obese patients.
Morantes-Caballero *et al.*,2019 [33]	Descriptive retrospective study	$PM_{2.5}$, PM_{10}	2016-2017 Colombia	250 103 M:147 F ≥65 years	Hospital Admissions	Patients with AECOPD have a higher median of particulate matter 48 hrs. prior to symptomatic onset, as well as greater use of antibiotics and corticosteroids.
Doneva *et al.*,2019 [30]	Multi-center, prospective, one-year observational study	SO_2, PM_{10}	2015-2016 Bulgaria	426 296 M:130 F >18 years	Hospital Admissions	Air pollution exposure led to an increased number of exacerbations and hospital stays. Patients with mild COPD had an average of 0.86 exacerbations and 2.61 days in hospital per year, while in those with severe COPD these values were 4 times higher. Outside pollution led to worsening of the disease

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						severity and hospitalizations due to COPD exacerbations.
Peacock *et al.*,2011 [79]	Cohort study	NO_2, O_3, SO_2, PM_{10}, BS	1995-1997 United Kingdom	94 All male ≥40 years	Respiratory response to shorter-term exposure of air pollution	Outdoor air pollution was associated with adverse effects on symptoms in patients with COPD.
Medina-Ramón *et al.*,2006 [80]	Case-crossover study	O_3, PM_{10}	1986-1999 United States	578,006 M:F(N/A) ≥65 years	Hospital Admissions	Exposure to O_3 and PM_{10} was associated with respiratory-related hospital admissions. The effect of air pollution was modified by city characteristics like meteorology, pollution sources, and socioeconomic factors.
Yang *et al.*,2005 [50]	Time-series study	NO_2, O_3, SO_2, CO	1994-1998 Canada	6,027 M:F(N/A) ≥65 years	Hospital Admissions	NO_2 and CO were significantly associated with hospitalization for COPD, and the magnitude of effects was increased slightly with increasing days of exposure
Stieb *et al.*,2009 [81]	Time-series study	NO_2, O_3, SO_2, CO, $PM_{2.5}$, PM_{10}	1990-2000 Canada	40,491 M:F(N/A) (>18 years)	Hospital Admissions	In this large multicenter analysis, daily average concentrations of CO and NO_2 exhibited the most consistent associations with ED visits for cardiac conditions, while O_3 exhibited the most consistent associations with visits for respiratory conditions.

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disease; BC: black carbon; BS: black smoke; CI: confidence interval; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; ED: emergency department; MI: myocardial infarction; NO_2: nitrogen dioxide; O_3: ozone; OR: odds ratio; PM_{10}: particulate matter less than 10μg/m^3 in aerodynamic diameter; $PM_{2.5}$: particulate matter less than 2.5μg/m^3 in aerodynamic diameter; SO_2: sulfur dioxide; RR: relative risk; SPM: suspended particulate matter; TSP: total suspended particles; UFP: ultrafine particles.

3.3. Influence of sex and age variables in the effects of short-term exposure to air pollution on AECOPD

Of the forty studies identified in this review, twenty-one reported the sex of the study participants, including one study enrolling only female patients [48], and one including all male patients [79]. In addition, seven studies reported AECOPD results disaggregated by sex [47,53,58,59,63,67,68], even though only four of these included the total number of male and female patients enrolled [47,53,58,68]. Overall, all studies found that there were significant associations between exposure to air pollutants and hospital admissions due to AECOPD.

A total of 426,630 hospital admissions for COPD were recorded in all 7 studies combined [47,53,58,59,63,67,68]. On average, there were approximately 409 admission counts per day, with males accounting for 72% (296 admissions) and females for 28% (113 admissions). After adjusting for potential confounders, SO_2, NO_2, and O_3 concentrations were significantly associated with increases in AECOPD hospitalizations in both sexes. Additionally, the relative risks (95%CIs) of AECOPD hospitalization in association with an

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inter-quartile range increase in air pollutants for 10 mg/m^3 increases in PM_{10}, SO_2 and NO_2, respectively were analyzed in single model in two studies [58,67]. In these, it was found that the relative risks of exposure to these pollutants were lower for males than for females, except for PM_{10} exposure.

Table 2 summarizes the descriptive statistics on the average AECOPD daily hospitalizations and the daily levels of the six environmental risk factors from the only 7 studies identified that compared male and female patient outcomes [47,53,58,59,63,67,68]. Six of these studies were conducted in China, and one in Brazil. Overall, all studies identified more male than female patients with AECOPD (42.3 males vs. 16.1 females on average) in the total population analyzed, although all studies also enrolled more male patients than female patients **(Table 2)**. In addition, while reporting results of AECOPD cases by sex, 3 of these studies failed to report the total number of male and female total patients enrolled [59,63,67].

In the only 4 studies reporting the number of male and female patients enrolled [47, 53, 58, 68], the percentage of patients that developed AECOPD was similar for both sexes in all but one study, where the hospitalizations for female patients were twice as high as those for males (0.39% vs. 0.18%, respectively, **Table 2**) [47]. Interestingly, this study reported some of the higher concentration averages for $PM_{2.5}$, PM_{10}, and SO_2 (60, 102, and 52 μg/m^3, respectively), as well as maximum values, when compared to the rest of the studies that also reported sex-disaggregated data **(Table 2).**

Table 2. Summary of daily hospital admissions for AECOPD in men and women, and 24-hour average air pollutant concentrations

	Studies						
	Du *et al.*,2021 [68] Jinhua, China (>65 years)	Cai *et al.*,2015 [63] Shanghai, China (>18 years)	Tao *et al.*,2014 [58] Lanzhou, China (>18 years)	Tian *et al.*,2014 [59] Hong Kong, China (>18 years)	Chen *et al.*,2019 [47] Shenyang, China (>65 years)	Liang *et al.*,2019 [67] Beijing, China (>18 years)	Arbex *et al.*,2009 [53] São Paulo, Brazil (>40 years)
Gaseous pollutants concentration (24 h average), mean (min-max)							
CO (μg/m^3)	0.7 (0.5-1.0)	1.3 (0.2-3.9)	NR	0.6 (0.1-2.1)	NR	1.2 (0.2-8.0)	2.7 (1.0-12.0)
NO_2 (μg/m^3)	28.0 (10.0-48.0)	61.0 (13.0-153.0)	45.8 (4.0-26.0)	40.9 (2.5-129.2)	43.0 (13.0-125.0)	50.5 (8.0-155.0)	120.3 (30.9-390.8)
SO_2 (μg/m^3)	7.2 (3.0-13.0)	53.0 (8.0-223.0)	79.1 (2.0-37.1)	NR	52.0 (3.0-333.0)	15.1 (2.0-139.0)	14.0 (2.1-42.9)
O_3 (μg/m^3)	84.5 (36.0-142.0)	NR	NR	NR	58.0 (9.0-218.0)	95.8 (2.0-292.0)	95.8 (14.5-282.0)
Particulate pollutants concentration (24 h average), mean (min-max)							
$PM_{2.5}$ (μg/m^3)	30.9 (14.0-57.0)	NR	NR	37.6 (6.8-163.2)	60.0 (4.0-848.0)	76.7 (5.0-467.0)	NR
PM_{10} (μg/m^3)	50.1 (25.0-84.0)	92.0 (12.0-643.0)	196.63 (16.0-256.1)	NR	102.0 (8.0-912.0)	109.7 (10.0-820.0)	48.7 (9.6-169.0)

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Patients with AECOPD (24 h average), mean (min-max)							
Male (% of total) (range) % of enrolled (n)	106 (81.5%) (73-144) 8.3% (1,277)	72 (64.9%) (10-231) N/A	2 (69%) (0-13) 0.05% (3,663)	46 (80.7%) (13-91) N/A	9 (52.9%) (0-16) 0.18% (4,920)	60 (67.4%) (9-153) N/A	0.9 (52.9%) (0-6) 0.09% (975)
Female (% of total) (range) % of enrolled (n)	24 (18.4%) (32-16) 8.4% (286)	39 (35.1%) (3-137) N/A	0.9 (31%) (0-6) 0.05% (1,638)	11 (19.3%) (0-34) N/A	8 (47.1%) (0-15) 0.39% (2,061)	29 (32.6%) (2-90) N/A	0.8 (47.1%) (0-7) 0.10% (794)
Total (range) % of enrolled (n)	130 (89-176) 8.3% (1563)	111 (14-368) 0.09% (121,463)	2.9 (0-13) 0.06% (5,301)	57 (17-117) 0.05% (117,329)	17 (0-31) 0.39% (4,409)	89 (17-220) 0.05% (161,613)	1.7 (0-10) 0.10% (1,769)

Abbreviations: AECOPD: acute exacerbation chronic obstructive pulmonary disease; PM_{10}- particulate matter of less than 10 microns in aerodynamic diameter; $PM_{2.5}$- particulate matter less than 2.5 microns in aerodynamic diameter; Min: minimum; Max: maximum; NR: not reported; N/A: data not available.

Regarding age, most studies enrolled patients over 18 years of age, except one study that enrolled patients over 40 [53] and two studies enrolling patients over 65 [47,68]. Combined, these studies revealed that the relative risk for AECOPD for patients aged ≤65 years is lower than that of patients aged ≥65 years **(Table 2)**. In addition, Tao *et al.* reported that the relative risk for COPD exacerbations was higher in elder females than males with increases in PM_{10}, NO_2, and SO_2 concentrations at lag 1-4 [58]. This concurs with results from previous studies suggesting that females and the elderly are some of the most vulnerable groups to outdoor air pollution [3,82-85].

3.3. Weather and geographic influences in air pollution effects on AECOPD

Studies conducted in different countries independently identified significant associations of temperature, humidity, and various air pollutants with hospital admissions in COPD patients. In a study conducted in Spain, de Miguel-Díez *et al.* found that COPD was negatively affected by colder climatological factors and exposure to O_3, CO, PM_{10} and NO_2 [77]. In a multipollutant model in Hong Kong, SO_2, NO_2, PM_{10}, and O_3 were also shown to display a greater effect on AECOPD admissions in the cold season (December to March) than in the warm season [52]. On the other hand, a study in Taiwan showed that during the warmer season, COPD exacerbations occurred more frequently on days of temperature increases than on other days [86]. Stieb *et al.* also found that associations tended to be of greater magnitude during the warm season (April - September) in seven Canadian cities during the 1990s and early 2000s [81]. Another study in Romania reported that the adverse effect of PM exposure on chronic bronchitis was reduced by higher humidity, and that dry air aggravated the adverse effects of PM exposure in COPD patients [49]. Finally, Du *et al.* found that O_3 was the most closely spatially correlated with AECOPD hospitalizations at sites located in the northwest region of Jinhua, China, likely due to many industrial complexes in this region [68].

3.4. Symptoms in the respiratory response to shorter-term exposure to air pollution

Regarding COPD exacerbation symptoms, most studies showed that COPD symptoms, but not lung function, were mainly associated with raises in air pollution levels. Of these, dyspnea was significantly associated with PM_{10} with an increase in odds for an interquartile range change in pollutant of 13% (95% CI 4% to 23%) which is one common approach to presenting multi-pollutant health effect estimates, and this association

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remained significant after adjustment for other pollutant exposures [79]. In addition, short-term exposure to traffic pollution was shown to prevent the beneficial cardiopulmonary effects of walking in individuals with COPD [70].

4. Discussion

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory lung disease involving chronic bronchitis and emphysema. Patients with COPD are particularly vulnerable to the detrimental effects of environmental exposures, especially from air particulate and gaseous pollutants. While sex and gender differences in COPD prevalence and severity have been previously reported, sex-specific effects of air pollution exposure on COPD exacerbations and hospitalizations have not been studied in detail. The available evidence indicates that outdoor air pollution exposure affects lung function and triggers exacerbations in both male and female COPD patients. However, in reviewing the literature, we found that most studies conducted in this area have not accounted for sex in their analyses.

Our review of the literature identified 40 studies measuring associations of air pollution exposures and AECOPD. In these, it was widely reported that increases in environmental particulate and gaseous pollution concentrations were associated with increased risk of hospitalization for AECOPD, with varying effects depending on air quality composition, pollutant concentration, and time of exposure. We found that the majority of these studies enrolled mostly male subjects, and some enrolled men exclusively. This was a surprising finding considering that the incidence of COPD among women has increased in the past few decades [3]. Potential factors that may contribute to this bias are the historical (although not current) higher incidence of tobacco use in men, occupational exposures, and the previously described gender bias in COPD diagnosis [10,11,87-89].

This study has several limitations. First, the number of studies identified by the selection criteria was limited and overrepresented in European and Asian countries, and the studies including or reporting participant data disaggregated by sex was markedly low, severely limiting the implications of our findings and our ability to conduct an analysis beyond descriptive. Second, our literature search was based on only two databases and including only studies in English, which could have omitted work available in other databases or languages, leading to selection bias. Third, using hospitalization rates as a comparison measure could also lead to bias, since hospitalization criteria may vary among countries and health systems, and since mortality associated with hospitalization for AECOPD does not always occur in the hospital.

This study has also several strenghts. First, it is the first review of the literature available assessing sex differences in an important outcome of the COPD pathogenesis and its relationship with air quality (i.e., hospitalization and mortality). Second, this study revealed a major gap in the research conducted to date in the area of COPD associations with air pollution in men and women, highlighting the importance of research design strategies that will identify sex- and gender- specific factors. Third, our review of the literature identified multiple studies where associations of air quality measures and AECOPD hospitalizations were reported, highlighting the importance of more research in these areas in order to design better preventative measures for COPD patients who live in geographical locations with poor air quality.

In the past few decades, the number of studies assessing the effects of air pollution exposure on lung disease has considerably increased [90]. However, studies considering sex (a biologic factor), or gender (a social construct, often used to refer to sex in publications) have been limited. Likewise, sex-specific disaggregation of data in the Global Burden of Diseases study has revealed that there are substantial differences between men and women that are frequently overlooked due to limitations in study designs [91]. This is highlighted by our findings in which only seven studies reported sex-disaggregated results, and only four studies had sufficient information to compare outcomes between male and female patients. Therefore, future studies should consider incorporating sex and

gender variables at the design stage, and perform sex and gender disaggregated results reporting and analysis.

5. Conclusions

In conclusion, the available literature indicates that air pollution exposure is a relevant risk factor for AECOPD hospitalizations, although there is a significant absence of studies assessing sex-specific effects in this area. This review emphasizes the need of more studies designed to address sex- and gender-specific effects of air pollution exposure, as well as studies including women, a vulnerable population.

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